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MONITORA DE ENSAIOS CLÍNICOS
UMA EXPERIÊNCIA DE 9 MESES

CLINICAL RESEARCH ASSOCIATE
A 9-MONTH EXPERIENCE

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor António José Monteiro Amaro, Professor Coordenador da Escola Superior de Saúde da Universidade de Aveiro.

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RESUMO

O principal objectivo do estágio na Eurotrials foi complementar os conhecimentos adquiridos durante a Licenciatura em Ciências Biomédicas e no Mestrado em Biomedicina Farmacêutica.

O estágio na Eurotrials pretendeu preparar o estagiário para trabalhar como Monitor de Ensaios Clínicos. Incluiu também uma visão geral sobre a forma de trabalhar e actividades desenvolvidas nos diferentes departamentos da empresa.

Todo o conhecimento previamente adquirido na Universidade foi complementado durante o estágio.

Este estágio de 9 meses como Monitora em treino foi uma excelente preparação para trabalhar na área dos Ensaios Clínicos e para isso contribuiu também a experiência transdisciplinar.

Continuar como colaboradora da Eurotrials irá proporcionar a oportunidade de realizar outras actividades que até ao momento não foram possíveis, consolidando os conhecimentos já adquiridos, permitindo o desenvolvimento de mais competências e maior autonomia.

ABSTRACT

The primary objective of the training in Eurotrials was to complement the knowledge acquired during the Degree in Biomedical Sciences and during the Master in Pharmaceutical Biomedicine.

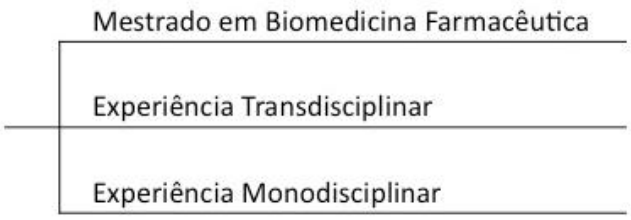
Eurotrials training program aimed to prepare the trainee to work as a CRA. It also included an overview of Company departments namely the working activities performed.

All knowledge previously acquired in the University was complemented during the training.

This 9-month experience as a CRA trainee was an excellent preparation to work in Clinical Trials and the transdisciplinar experience greatly contributed to this preparation.

Continuing as a collaborator at Eurotrials will give the CRA trainee the opportunity to perform other activities not yet experienced, to consolidate know-how and to get more experience as well as to become more autonomous.

SINOPSE

Título do Estágio:	Monitora de Ensaios Clínicos - uma experiência de 9 meses
Objectivos:	O principal objectivo do estágio na Eurotrials foi complementar os conhecimentos adquiridos durante a Licenciatura em Ciências Biomédicas e o Mestrado em Biomedicina Farmacêutica. O estágio na Eurotrials pretendeu preparar o estagiário para trabalhar como Monitor de Ensaios Clínicos. Também incluiu uma visão geral sobre a forma de trabalhar e actividades desenvolvidas nos diferentes departamentos da empresa.
Duração do Estágio:	9 meses
Período do Estágio:	06 de Setembro de 2010 (data de início do estágio) 06 de Junho de 2011 (data de conclusão do estágio)
Desenho do Estágio:	
Coordenação:	Luís Almeida (Director do Mestrado em Biomedicina Farmacêutica) António Amaro (Orientador/Professor Coordenador da Universidade de Aveiro) Susana Bule (Co-orientadora/Directora Executiva da Eurotrials) Raquel Reis (Responsável pelo Departamento de Ensaios Clínicos da Eurotrials) Graça Silveira (Gestora de Projecto) Isabel Pinto (Gestora Operacional de Monitores)
Relatório de Estágio escrito por:	Maria Inês Cabral
Conclusões:	Todo o conhecimento previamente adquirido na Universidade foi complementado durante o estágio. Este estágio de 9 meses como Monitora em treino foi uma excelente preparação para trabalhar na área dos Ensaios Clínicos e para isso contribuiu também a experiência transdisciplinar. Continuar como colaboradora da Eurotrials irá proporcionar a oportunidade de realizar outras actividades que até ao momento não foram possíveis, consolidando os conhecimentos já adquiridos, permitindo o desenvolvimento de mais competências e maior autonomia.

SYNOPSIS

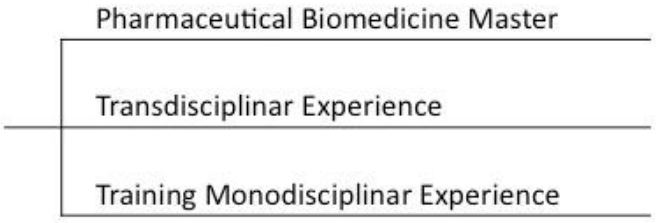
Training Title:	Clinical Research Associate (CRA) – a 9 month experience
Objectives:	The primary objective of the training in Eurotrials was to complement the knowledge acquired during the Degree in Biomedical Sciences and during the Master in Pharmaceutical Biomedicine. Eurotrials training program aimed to prepare the trainee to work as a CRA. It also included an overview of Company departments namely the working activities performed.
Training Duration:	9 months
Training period:	6th September 2010 (training initiation date) 6th June 2011 (Training completion date)
Training Design:	
Coordination:	Luís Almeida (Pharmaceutical Biomedicine Master Director) António Amaro (Supervisor/ Coordinator Professor of University of Aveiro) Susana Bule (Co-supervisor/Executive Director of Eurotrials) Raquel Reis (Eurotrials Head of Clinical Trials Department) Graça Silveira (Project Manager) Isabel Pinto (Line Manager)
Training Report performed by:	Maria Inês Cabral
Conclusions:	All knowledge previously acquired in the University was complemented during the training. This 9-month experience as a CRA trainee was an excellent preparation to work in Clinical Trials and the transdisciplinar experience greatly contributed to this preparation. Continuing as a collaborator at Eurotrials will give the CRA trainee the opportunity to perform other activities not yet experienced, to consolidate know-how and to get more experience as well as to become more autonomous.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition/Explanation
CA	Competent Authority
CEIC	Ethics Committee for Clinical Research
CNPD	Portuguese Data Protection Authority
COTEC	Business Association for Innovation
CRA	Clinical Research Associate
CSA	Clinical Study Agreement
CT	Clinical Trial
CTA	Clinical Trial Assistant
CTMS	Clinical Trial Management System
CRF	Case Report Form
CRO	Clinical Research Organization
DDD	Data Definition Documentation
DMD	Data Management Department
DMP	Data Management Plan
DMQC	Data Management Quality Controller
DQCR	Database Quality Control Report
DSD	Database Support Documentation
DVP	Data Validation Plan
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration

FQ	Feasibility Questionnaire
FSA	Feasibility Study Assessment
IAPMEI	Institute for the Support of Small and Medium-sized Enterprises
ICF	Informed Consent Form
IF	Investigator File
IM	Investigator Meeting
IMP	Investigation Medicinal Product
INFARMED	National Authority of Medicines and Health Products, IP
IP	Public Institute
ITS	Information Technology Specialist
IVRS	Interactive Voice Response System
ORL	Otorhinolaryngology
PI	Principal Investigator
PhF	Pharmacy File
R&D	Research and Development
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Data Set
SDV	Source Data Verification
SIV	Site Initiation Visit
SME	Small and Medium-sized Enterprise
TMF	Trial Master File
UKAS	United Kingdom Accreditation Service
WHO	World Health Organization

2. INTRODUCTION

2.1. TRAINING OBJECTIVES

The main objective of this 9-month training was to prepare the trainee in the best working practices to work as a Clinical Research Associate (CRA) and to consolidate the knowledge acquired in the Degree and Master through practical experience.

Moreover, considering the Company organization, additional objective was to be able to interact with other areas of expertise, namely Data Management and Biostatistics, in order to gather know-how related with information flow and processes that are also crucial for the CRA performance.

2.2. STATE OF THE ART

According to the Office of Technology Assessment[(1)], Pharmaceutical Research and Development (R&D) is the process of discovering, developing and bringing to market new drug products. This process is influenced by science and economy, while the first one defines opportunities and constrains, the second one decides which opportunities and scientific experiments will be target of industrial research. Investors determine if they will invest in a research project according to investment's costs and risks.

Drug discovering processes have changed over the years. At the beginning of medicines history, products came from nature. The method "try and error" was used, the reason behind those effects was not known and anyone could try the drug.

"Physicians pour drugs of which they know little, to cure diseases of which they know less, into humans of which they know nothing" by Voltaire, c. 1760.

With the evolution of medicine, new approaches appeared and nowadays, the process of drug discovery and development is strictly regulated and several steps are needed for drugs to become available to anyone.

In the 1990s, genetic engineering, computer modelling and biotechnology had a great impact in R&D processes. Computer modelling became essential due to its capability of predicting how a molecule will work in human body. It allows virtual manipulation of a molecule in order to enhance its activity and understands the relation drug-receptor. This will reduce costs of synthesizing molecules that will not pass in future tests. This advantage is only possible due to the great improvement of diseases mechanisms knowledge.

When drug synthesis phase starts, the major objective is to select the best route of administration of substances and know how they react in different conditions and with different reagents. Stability, pH, solubility, biocompatibility with organic solvents are examples of characteristics that needed to be identified in order to predict drug absorption and distribution *in vivo* and for studies of structure–activity relationship, which may direct future synthesis[(2)].

This *in vitro* step of R&D process includes a huge number of tests and results in some compounds that are considered to have potential as a new medicine. The next step is the *in vivo* testing, which includes preclinical and clinical trials.

According to Griffin[(3)], during the R&D process of a potential new pharmaceutical compound, proving quality, efficacy and safety of the potential new drug are the primary objectives. In what concerns safety, compound risks must be inferior to benefits. Preclinical trials are important to predict the range of safe exposures to the drug and to identify the risks involved in the overdose of this safety range.

Preclinical trials importance has increased after Thalidomide event. Nowadays there is legislation requiring several preclinical tests before a drug is administered into humans. These tests include[(4)]:

- Biochemical-pharmacological studies (analysis of drug binding to

receptors, understanding the kinetics of interaction and the characteristics of the binding site itself).

- Pharmacokinetics studies (in order to obtain information regarding absorption, distribution, metabolism and elimination of the drug).
- Toxicological investigations to evaluate the potential for:
    - Toxicity associated with acute or chronic administration
    - Genetic damage (genotoxicity, mutagenicity)
    - Production of tumors (oncogenicity or carcinogenicity)
    - Causation of birth defects (teratogenicity).

Preclinical trials induce a great reduction of the number of drugs with potential to be used in humans due to all required specificities that substances must meet in order to be administered in man. After the minimum required information is obtained, clinical trials can begin.

According to the *World Health Organization* (WHO), "a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc"[5].

Typically, clinical trials can be grouped in 4 phases[6, 7]:

- **Phase I** – Human Pharmacology
    - "First in man studies"
    - 20-80 subjects that are usually healthy volunteers but occasionally may be patients with the targeted disease.
    - Help determine how the human body will handle the drug (pharmacokinetics), how the drug will behave within the human body (pharmacodynamics) and what doses to use for Phase II clinical studies (e.g., side effects associated with increasing doses).
- **Phase II** – Therapeutic Exploratory
    - Use patients (usually several hundred) with the disease or condition

that the drug is intended to treat.
    - Typically well controlled, generate early data on the drug's efficacy and safety while being used to treating the particular disease.
- **Phase III** – Therapeutic Confirmatory
    - Called pivotal trials: the trial will determine whether a new drug is inferior, equivalent, or superior to the standard treatment.
    - Usually consisting of hundreds to thousands of patients.
    - Aim to prove a drug's effectiveness and safety (positive benefit/risk balance).
    - Help predict how the drug may behave in the general population and establish the information that will appear on the drug label.
- **Phase IV** – Therapeutic Use
    - Drug is already approved and marketed.
    - Can provide more information on the drug's effectiveness and safety in real-life conditions and either confirm or add indications to a drug's label.
    - Refine understanding of benefit/risk relationship in general or special populations and/or environments.

As described in ICH guideline E8, studies do not have to respect a temporal order, study objectives are more important, "new data may suggest the need for additional studies that are typically part of an earlier phase"[6].

After obtaining all required information about the drug and before starting phase IV clinical trials, a market authorization application can already be submitted. Every country has a national authority responsible for the evaluation of drugs and their submission applications. In Portugal, the national authority is INFARMED (National Authority of Medicines and Health Products, IP) being also the local representation of the European Medicines Agency (EMA) while in the United States of America is the Food and Drug Administration (FDA) and in Canada is the Health Protection Branch Drugs Directorate. In the European Union there are 4 different procedures to obtain a market authorization[8, 9]:

- **Centralized** – the authorization is valid in all European Union member states. The application is evaluated by EMA, which has a group responsible for the scientific evaluation of the application (Committee for Medicinal Products for Human Use). The European Commission reviews the evaluation and adopts a decision.
- **Decentralized** – only possible when the product has no previous market authorization in any member state. The submission occurs simultaneously in various member states but one will be responsible for the elaboration of an assessment report (reference member state). Based on this report and comments made by member states, the authorization will be obtained or not.
- **Mutual recognition** – when a market authorization for a product has been obtained in a member state and other member states can approve or not the decision made by the first member state, recognizing its decision.
- **National** – The competent authorities of the Member States are responsible for granting marketing authorizations for medicinal products, which are placed on their markets.

When the market approval is obtained, the real test of the drug starts since anyone can take the product and for most cases there are no studies for the real environment where the drug will be administrated. This is the major limitation of clinical trials due to the close monitoring existence and to the restricted inclusion and exclusion criteria that studies patients must have to participate in the trial.

Figure 1 represents a scheme where the process of drug development is described, beginning with compounds synthesis to drug approval and introduction in the market[(4)]. It gives a clear idea on the number of potential compounds that will be screened during this process, ending with the best compound among 10000 substances that started the preclinical testing phase.

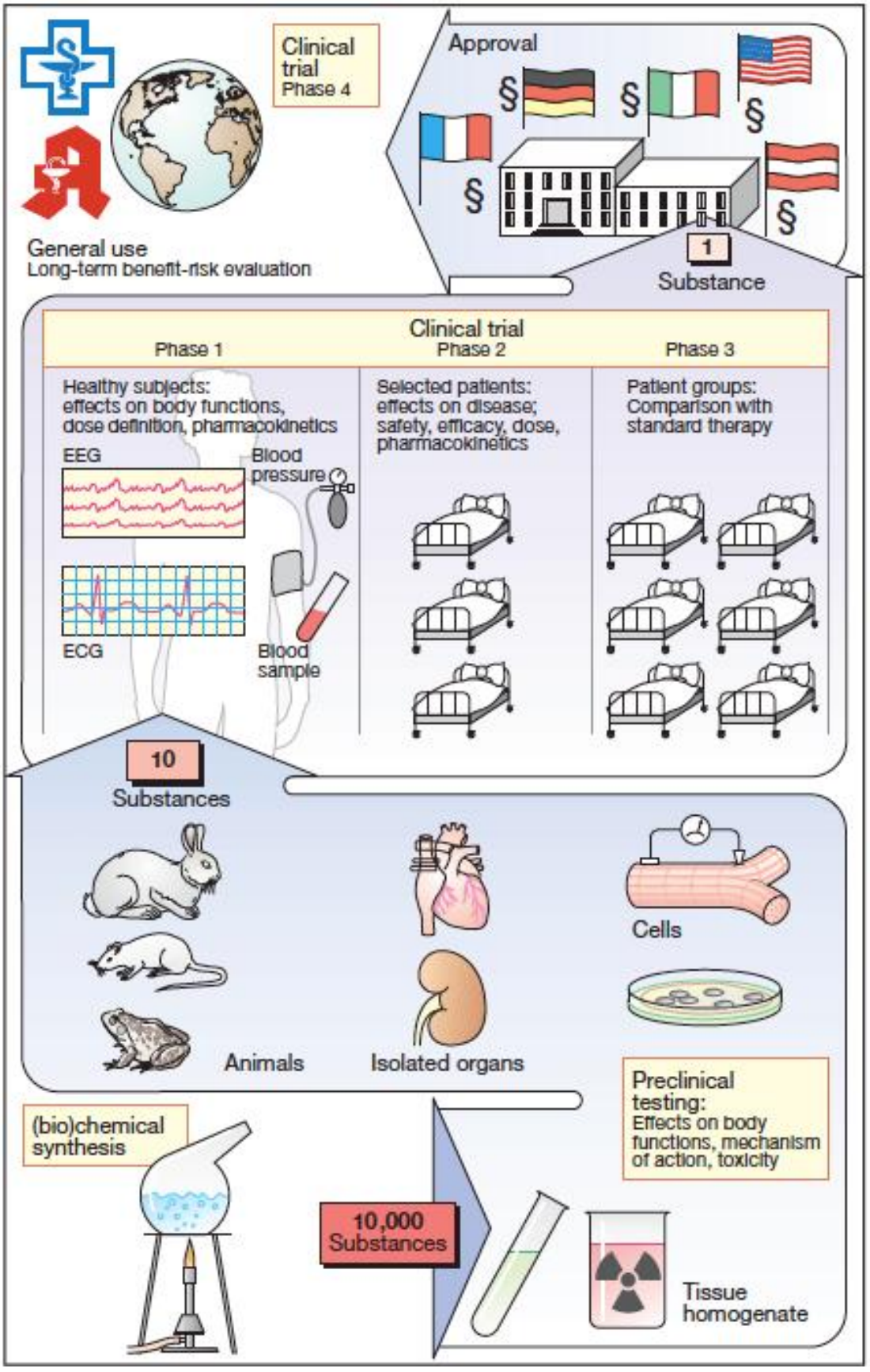


Figure 1 - From drug synthesis to approval.

Ethical issues regarding human safety during the history of medicine and pharmaceutical industry created the increased need of control and regulate R&D all the processes with special attention to animal and human protection issues. The Nuremberg Code, Helsinki Declaration, ICH guidelines, local, European and FDA legislations are the main reference for the standard procedures in clinical research.

In Portugal, INFARMED, Ethics Committee for Clinical Research (CEIC) and the Portuguese Data Protection Authority (CNPD) are responsible for the evaluation and approval of a clinical trial. INFARMED is responsible not only for the approval of clinical trials but also for all other issues related with medicines and their use in the national territory.

National Legislation includes local requirements and the transposition of several European directives. Some of the more important Portuguese requirements in medicines for human use are described in the Decree-law no. 176/2006 of August 30 (known as the Medicinal Product Statute), in the Law no. 46/2004 of August 19 (known as the Clinical Trials Law) and in Decree-law no. 102/2007 of April 2 (known as GCP Directive).

3. VISION ABOUT THE INSTITUTION – EUROTRIALS

Established in Lisbon in 1995, *Eurotrials, Scientific Consultants*, is a private owned company specialized in clinical research and scientific consultancy in the Health area.

Currently, the company has it Head Quarters in Portugal, one office in Brazil, a local representation in Chile and Argentina. Eurotrials is also present through partners in other countries of Europe, and has some collaborations in Portuguese-speaking African countries. This success "stands on pillars that have marked its personality since it was founded: creativity in finding solutions, unique technology, multidisciplinary expertise, solid experience and quality. It is qualified to participate in each and every step clinical, translational or epidemiological research project, from start of the research until the Final results are available"[(10)].

In Portugal, Eurotrials is recognized and certified by different entities[(11)]:

- **ISO** - certified by ISO 9001 since 2001 throw Lloyd's Register Quality Assurance with United Kingdom Accreditation Service (UKAS). After that, in 2002 and 2008 it was obtained the certification to ISO 9001:2000 and ISO 9001:2008, respectively.
- **"Rede PME Inovação COTEC"** – since 2007, Eurotrials belongs to this group of Small and Medium-sized Enterprises (SMEs) recognized by their innovative attitude and activities, which make them an example of creation of value for the country.
- **Leading SME** – the Institute for the Support of Small and Medium-sized Enterprises (IAPMEI) considered Eurotrials in 2007 as a leading SME due to their quality of performance and risk profile.

Nowadays, Eurotrials aims to achieve the following objectives[(12)]:

- Continue to develop innovative Clinical Research projects.
- Bridge the gap between Basic, Academic Research and market – Translational research.

- Interact with Institutional Research Groups for the potential development of therapeutic alternatives, medical devices and other innovative approaches.
- Promote the development of a network of centres of excellence.

In Portugal, the company performs several activities during R&D process, which are represented in Figure 2[12].

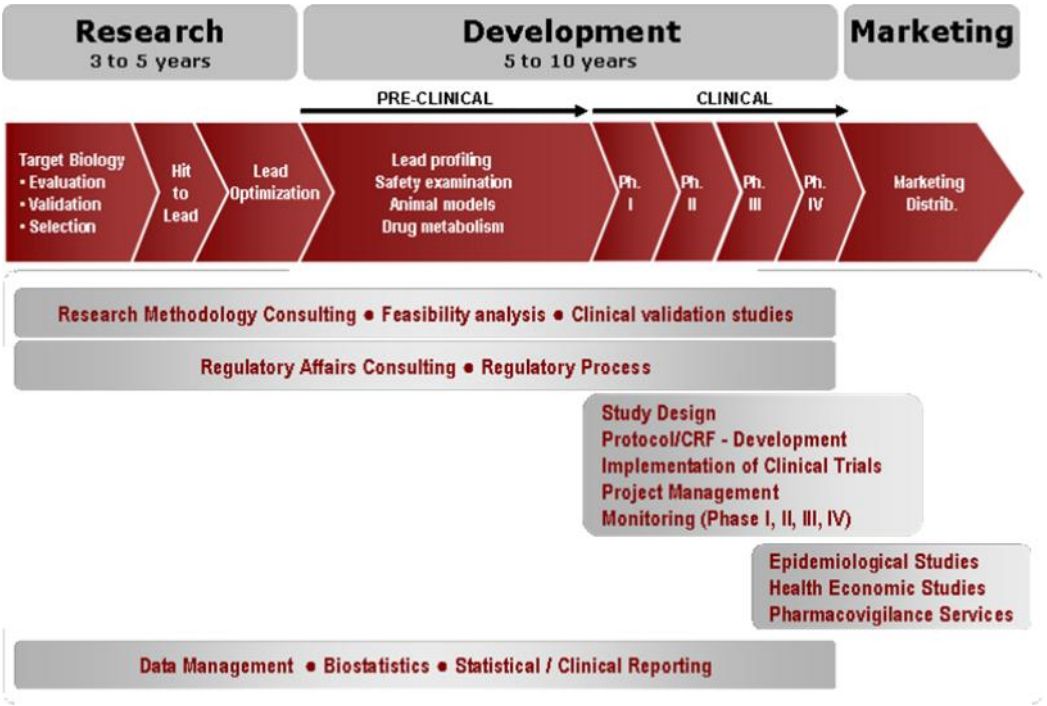


Figure 2 - R&D Eurotrials activities.

In order to be able to perform its services and activities, Eurotrials is organized in the following departments, which communicate and interact with each other on a daily basis (Figure 3[13]):

- Research and Development
- Clinical Trials
- Epidemiology & Late Phase Research
- Data Management
- Biostatistics
- Regulatory Strategy & Affairs

- Pharmacovigilance
- Pharmacoeconomics
- Quality
- Teaching and Training

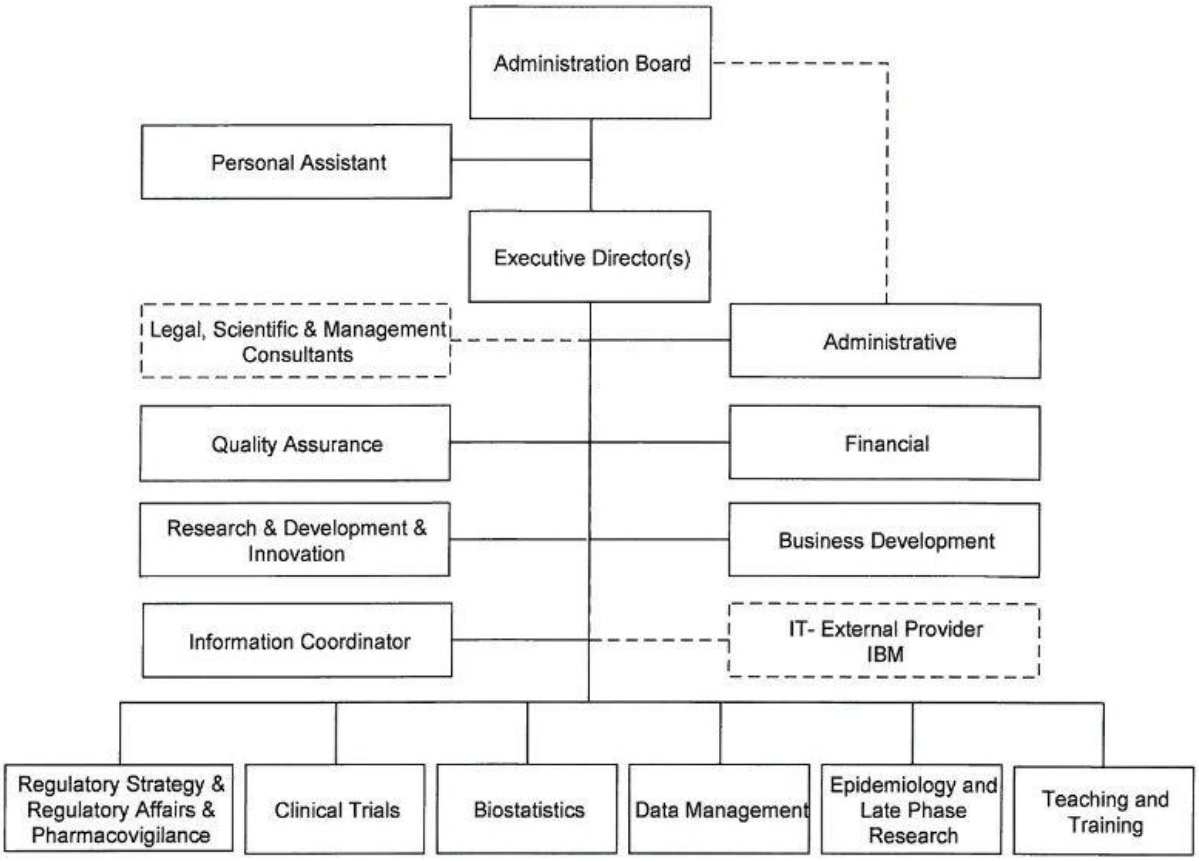


Figure 3 - Eurotrials organogram.

4. TRANSDICIPLINAR EXPERIENCE

The training program developed at Eurotrials involved close interaction with two departments within the company: Data Management and Biostatistics. These departments have different roles, which are explained in sections 4.1 and 4.2, respectively.

A summary of the developed activities by Data Management and Biostatistics departments are presented in Table 1.

Table 1 – Activities developed by Data Management and Biostatistics Departments.

Data Management	Biostatistics
• Clinical Data Management System • Database Development • Data Entry (remote or in-house) • Data Verification • On-going Data Management • Clean Database • Database Quality Control • Database Reports	• Study Protocol Support • Statistical Analysis Plan • Statistical Analysis • Statistical Report • General Consultancy • Support on Medical Writing

4.1. DATA MANAGEMENT

The Data Management Department (DMD) has an important role in the transfer of information recorded within the Case Report Form (CRF) into clean and validated data that will be consequently analysed by Biostatistics.

A training meeting was organized to explain how the department was structured, which, when and how activities were developed. It allowed trainee to understand how relevant and interesting these activities are in a clinical trial and mainly, what Data management process is.

Within this department range of activities, there are specialists from different areas of expertise namely, Information Technology Specialists (ITS), Database

Operators, Data Managers and Medical Reviewers. It is possible to understand all activities developed by DMD through Figure 4[13]. This figure explains Internal Department organization that is aligned with the circuit of data since its inclusion in the system, by a Data-Entry Operator until the evaluation by a Data Management Quality Controller (DMQC).

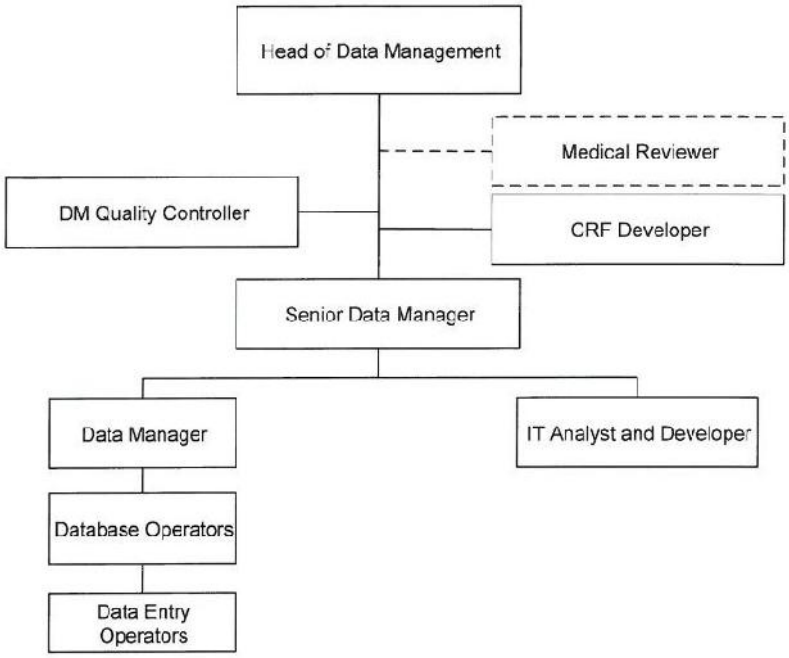


Figure 4 - Data Management Department Organogram.

The relation of this team with a clinical trial/epidemiological study involves in many instances the design and development of CRFs, either on paper or electronic format. In all most cases, when this department is contracted to manage the data, they are also responsible for the development of the CRF. For this activity to be duly accomplished, it is important to know and understand the study protocol and main variables in order to be able to introduce all necessary fields within the CRF and not needless ones.

Within a specific clinical study, the workflow since the design of the CRF until the sending of cleaned data to Biostatistics Department/team includes several steps which are explained bellow and summarized in the Figure 5.

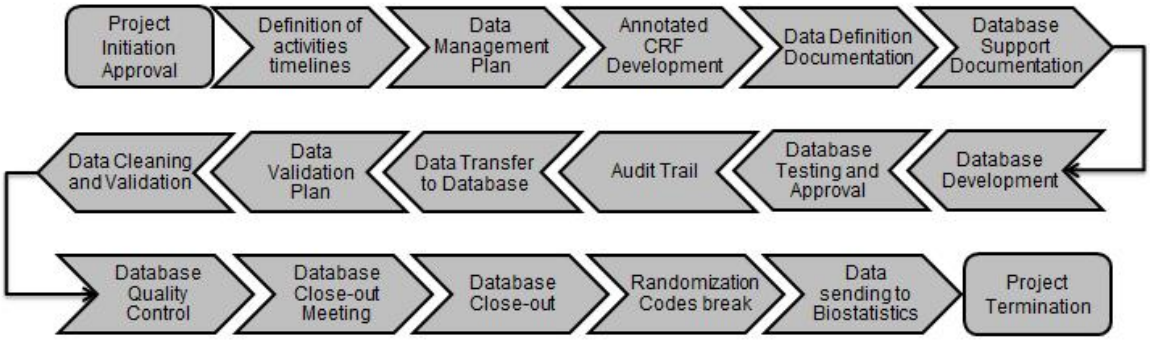


Figure 5 - Data Management workflow.

1. Definition of activities timelines

Before the CRF development begins, it is essential to define the activities to be performed as well as the timelines for each activity in order to ensure the delivery of the product to the client within the pre-defined timelines and according to agreed specifications.

2. Data Management Plan

Data Management Plan (DMP) defines all the issues that will be important and helpful on the handling of data. It must include, at least, internal management rules, study team and how the DM study team will create and organize their Trial Master File (TMF).

3. Annotated CRF Development

The Annotated CRF is an important document used by all team members and describes all variables/fields within the CRF. It maps each item on the CRF to the corresponding variables in the database.

4. Data Definition Documentation

The Data Definition Documentation (DDD) is an especially useful document for data integration in other database(s), as safety databases.
The DDD is a technical document that specifies all database tables/modules (datasets), its fields and the code lists used for database development.

Therefore, all database fields are described according to its attributes: type (numeric or alphanumeric), description (label), size and code list association.

5. Database Support Documentation

The Database Support Documentation (DSD) includes the Annotated CRF and the Data-entry Manual. The DSD states the pre-defined rules and procedures that must be followed during data transfer to database.
This document is essential not only for data-entry procedures but also to Data management and statistics activities (namely the Annotated CRF).

6. Database Development

For any given study, a specific database needs be developed. This database must have into consideration the CRF structure. Therefore, all data entry screens will be developed in order to emulate the CRF pages and datasets will be assembled according to the pre-established requirements stated in the DDD.

7. Database Testing and Approval

Database testing is performed preferentially with real data. The objective of this activity is to find the major number of errors/inconsistencies among the CRF fields to prevent them from occurring when the CRF is in use and data is entered. From these tests, a Functionality Report is written describing all detected findings.
The Data Manager is the person responsible for correction/solving all reported findings. Then, in order to guarantee that findings were identified and duly corrected, a form must be signed by Data Manager and DMQC (who performed these tests) and filled.

8. Audit Trail

Audit trail is an electronic record that tracks the data life-cycle in database. It reports who has introduced/changed the data, when it occurred, what was updated (old value/new value) and the reason for changing/correcting the data.

This electronic record is validated according to FDA 21 CFR part 11 rule of the Code of Federal Regulations. This document defines “the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper”[(14)], i.e., if the requirements are met, the electronic records can be used in lieu of paper records.

9. Data Transfer to Database

After Database approval and before any data-entry activity, training must be given to Data-entry staff on the use of the Database and related documents.
The data transfer to database will be performed according to specific rules pre-defined in the DSD. These specific rules include the handling of missing data (not done, not known, not applicable and not available) where a specific notation is attributed according to the type of missing data.

Table 2 – Notations attributed according to the missing data.

Type of Missing Data	Correspondent Notation for:	
	Alphanumeric Fields	Numeric Fields
Not Done	N/D	-1
Not Known	N/K	-2
Not Available	N/AV	-3
Not Applicable	N/A	-4

10. Data Validation Plan

Data Validation Plan (DVP) is a document that lists all checks needed to be performed in order to detect discrepancies in study data. It also describes the type of validation that each field needs: automatic or manual. Typically, about 90% of all fields represent data that is automatically verified and only 10% needs manual analysis. The Study Protocol, CRF and laboratory normal ranges are

essential for the DVP development. It is prepared by a Data Manager outside the study and approved by the study Data Manager.
DVP is used in data cleaning and validation. Although this process requires a multidisciplinary team involvement in order to assure cross-checks accuracy, the Study Data Manager is the final responsible for data validation.

11. Data Cleaning and Validation

According to the data entry type (double or simple), there are different stages of data cleaning. Double entry means that there are two persons introducing the same information in the system in order to reduce the probability of transcription errors while simple entry means that there is only one person introducing the information in the system.
The data cleaning and validation stages are: data entering, data cleaning (is only done in case of double entry and the objective is to obtain a simple entry through the confirmation that the data entered by the two persons is the same), data validation, and issue of queries. The objective of queries can be: to confirm, clarify or complete information.
The final objective is to obtain correct and complete data and, if necessary, the steps can be repeated until questions are solved. After this, all deviations to the protocol are listed and classified as Major or Minor by Sponsor or Data Management Team and data to be eliminated is identified in the end of this phase.

12. Database Quality Control

Before the database lock, it is important to classify errors in three categories according to the influence in study results:

- A - when the error does not change the meaning of data
- B - when the error changes the meaning of data
- C - when the error changes the meaning of data related to study objectives (errors from type C should not exist, however if these occur they should be corrected).

Study Data Manager and DMQC write a Database Quality Control Report (DQCR) describing all errors found between study data and the database. Any deviations identified are classified in quantity and quality (A, B or C).

13. Database Close-out Meeting

This meeting is performed in order to review deviations classification and to confirm that the database is ready to be closed. In this meeting all the team members should be present, as well as a statistician and a sponsor representative.

14. Database Close-out

Authorisation from Sponsor is needed to close the database. After its closure, if an error/problem occurs and is necessary to re-open the database, authorisation from Sponsor is required. Besides special cases, this situation should be avoided as this is the final step before clean data release to Biostatistics or Client.

15. Randomization Codes break

The codes can only be opened after database close and this must always be recorded in a specific form. The codes are introduced in a program named Statistical Analysis data Set (SAS) and a table is developed with information regarding treatment groups and medication administrated in each group.

16. Data sending to Biostatistics

The last responsibility of the Data Management Team is to deliver all cleaned data obtained to Biostatistics Department. After this, some clarifications may be needed and they must always be available to help biostatisticians.

4.2. BIOSTATISTICS

Biostatistics Department is constituted by some statisticians with different level of knowledge and experience and also by a Senior Consultant (Figure 6[13]).

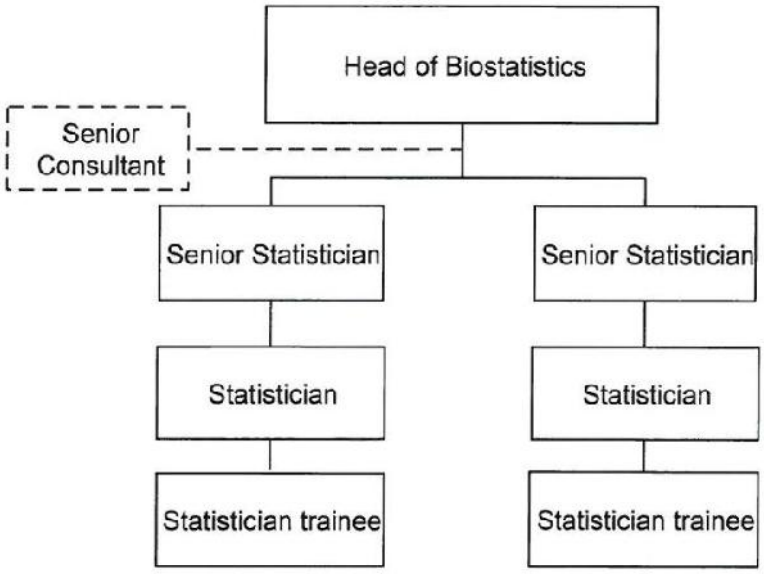


Figure 6 - Biostatistics Department Organogram.

Through a training meeting, activities performed by this Department as well as its organization were explained to the trainee. It allowed the CRA trainee to understand the importance and clear impact that Biostatistics have on other Eurotrials departments' activities (schematized in Figure 7), namely in the following areas:

Clinical Trials

The preparation of protocol methodology sections, Statistical Analysis Plans (SAPs), statistical reports and randomization lists/codes are the main areas of involvement of this department in the Clinical Trials.

Epidemiology & Late Phase Research

In what concerns this department, Biostatistics prepares the methodology section of protocols, statistical reports (usually just objectives, methodology and results) and databases.

Data Management

The relation between these two departments includes the sending of cleaned data in different formats (Access, SAS or Excel) from Data Management to Biostatistics in order to allow the statistical analysis of the information obtained during clinical trials and epidemiologic studies.

Pharmacoeconomics

The role of Biostatistics in the Pharmacoeconomics department includes the search of bibliography information, revision/elaboration of electronic models that will be needed to analyse collected data, preparation of questionnaires, help in the conduction of Expert Panels, analysis, treatment of data and finally, elaboration of a report.

There are three Expert Panel methodologies[15]:

- **Delbecq** – a face-to-face meeting is organized with all selected experts, in order to discuss the questionnaire topics. A member of Eurotrials orients the meeting and the final objective is to achieve a consensus about the topics for the questionnaires.
- **Delphi** – each expert panel member receive a post questionnaire. After receiving the answered questionnaires, Eurotrials prepares a consensus questionnaire after statistical data analysis of data. The new questionnaire is then sent again to experts in order to approve the conclusions. It may be necessary to perform this circuit several times until a consensus is obtained.
- **Key-informers** – a personal interview with each expert panel member (Key-informer) is performed in order to know their opinion in a particular subject. After all interviews, Eurotrials analyses the data, obtaining estimates that are used to build a consensus questionnaire. This is then sent to experts in order to approve the conclusions. As in the Delphi method, the questionnaire may need to be changed and consequently revised, several times.

The Sponsor should choose which methodology wants to use. Eurotrials usually advises to use the Delbecq method due to the greater robustness of estimates obtained through a face-to-face meeting.

Teaching and Training

Universities, private organizations and even doctors, usually contract Eurotrials, to provide training in different areas, including statistics. In this area, there are courses focused on practice of statistics (basics and more specific approaches), interpretation of results and also on how to perform clinical trials sample calculation.

Regulatory Strategy & Affairs

One of the Regulatory Strategy & Affairs department roles is to evaluate the readability of Patient Information Leaflets. Biostatistics, in this activity, helps to prepare the questionnaire used to evaluate if the information in the leaflet is adequate and in the end analyses if the results are favourable.

Medical Writing

The elaboration of articles, posters, power point presentations, and others, also needs the help from this department in sections like methodology, results and conclusions.

Other activity performed by this department is the elaboration of trimestral Newsletters (“Boletins Informativos”) regarding different therapeutic issues and in which is done an evaluation of the worldwide situation of the disease, for example.

In order to better understand how this publication is developed, it was asked to the CRA to help prepare the document. CRA involvement included the bibliography research and the initial written of the newsletter. It was understood that this is a very challenging activity due to lack of credible available information and to the difficulty of finding information for all countries in the world.

Figure 7 - Interactions between Biostatistics and other Eurotrials departments.

5. MONODISCIPLINAR EXPERIENCE

5.1. CLINICAL TRIALS MONITORING

Eurotrials Clinical Trials department was the first department to be created and is the biggest department of the Company. Its organization is complex and due to the contact with different clients/sponsors, people of this team have the opportunity of acquire knowledge in several work environments according to: clinical trial therapeutic area and phase, client/sponsors rules/procedures and training structure.

In Figure 8[13] is represented the department organogram in which is possible to observe that the global team is divided into groups leaded by Line Managers. In each group, there are CRAs with different levels of knowledge and at the base there are Clinical Trial Assistants (CTAs) that give administrative support to CRAs. The organogram also represents the possible career progression within the CRA role.

The Start-Up Team is responsible for the clinical trial application to the several national authorities as well as for the preparation and negotiation of clinical study agreements/study contracts with Principal Investigators (PIs), sites and sponsors.

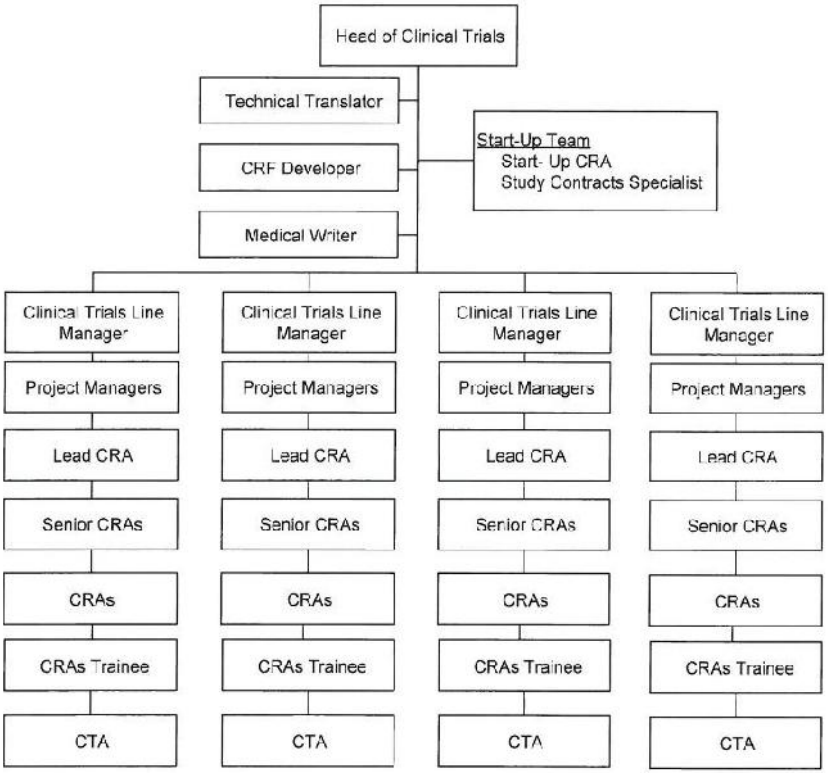


Figure 8 - Clinical Trials Department Organogram.

Since 1996, this department has been involved in a large number of clinical trials, being Cardiology and Oncology the therapeutic areas with more studies. This historical data is consistent with the status of the art where these areas represented the major health problems for which Pharmaceutical Companies invested more along the years. Nowadays, main trials are focused on Oncology and Neurology (Figure 9[12]).

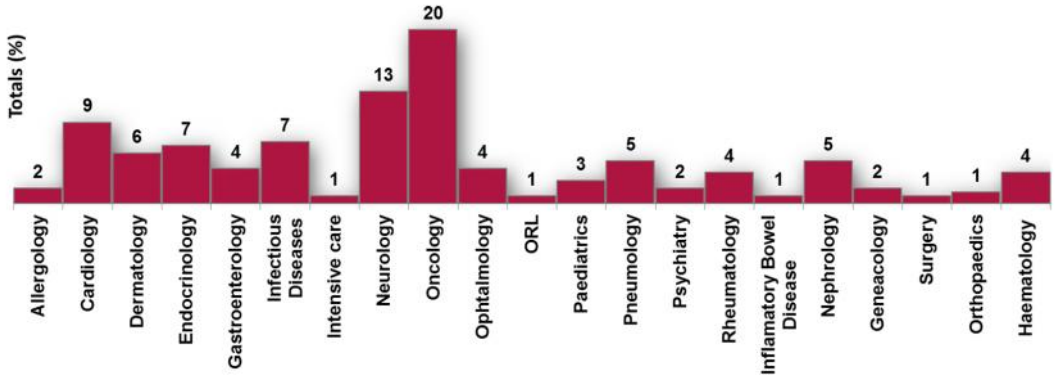


Figure 9 - Distribution of clinical trials performed by Eurotrials (data between 1996 and December 2010), according to the therapeutic area.

In what concerns the phases of clinical trials conducted at Eurotrials, Figure 10[12] allows to conclude that phase III is the most common type of studies (69%) while phases I represents the lower percentage (1%).

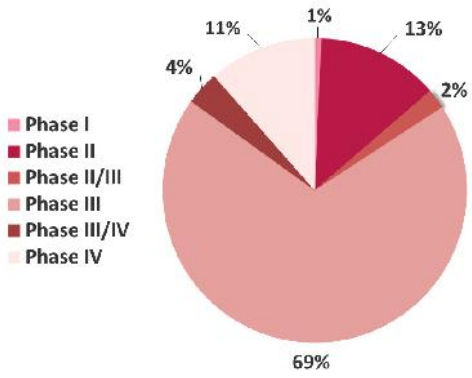


Figure 10 - Distribution of clinical trials performed by Eurotrials (data between 1996 and December 2010), according to the study phase.

5.2. DEVELOPED ACTIVITIES

During the 9-month experience as a CRA trainee in Eurotrials clinical trials department, it was possible to work in several clinical trials as well as learning with the different working methodologies of the different CRAs and Sponsors.

5.2.1. Confidentiality

Pharmaceutical Industry is a very competitive business area and significant expenditure is made every year in R&D processes. In order to ensure appropriate disclosure of confidential information, every collaborator has to sign a Confidentiality Agreement before starting its functions in the company. This agreement has an enhanced importance in Clinical Research Organizations (CROs) due to their several different clients, which increases the probability of dealing with confidential, sometimes competitive, information.
In this area of activity, Confidentiality is a mind-set of good practices and a "way of living" that is evidenced through the signature of the Confidentiality Agreement. This is the first action of any collaborator joining Eurotrials and as CRA trainee this document was signed before starting the activities in Eurotrials.
This signed agreement created restrictions on the information to be included by the CRA trainee in the Training Report, namely clients/sponsors identification, names of Investigational Medicinal Product (IMP) or clinical trials acronyms could not be used.

5.2.2. Training

Every new collaborator that joins Eurotrials must follow a Training Program related with the role that will perform in the company.
Such trainings may be categorized as:

- **Job Specific**

This training requires the reading and understanding of Eurotrials Quality Manual, Integration Manual, SOPs and additional reference documents (e.g. ICH-GCP, European directives, local legislation, among others) relevant to the job

description/function of the CRA as per the Company Training Matrix. In what concerns the company SOPs, some SOPs are mandatory to all collaborators but others are specific to each job description.

In addition to the job initial training that every new collaborator performs, there is an Annual Training Plan, which aims to assure staff continuous training and quality of the activities developed. There is a constant assessment of training needs within Eurotrials so the Company Annual Training Plan include as much as possible such training needs. This plan may be updated with new identified training needs whenever justified.

- **Project Specific**

For each study it is essential to have Project Specific Training. Such training covers at least the following topics: Therapeutic area, Protocol, Monitoring Manual, Communication Plan, CRF, Informed Consent, study procedures, project applicable SOPs and related forms, either from Sponsor or CRO.
Upon Sponsor agreement, the responsible CRA always made a brief introduction to the CRA trainee before starting any study activities.

During this 9-month period there was the opportunity to have training in several studies from different Sponsors. In addition to the topics highlighted above, there was also the opportunity to perform additional project specific trainings like in InForm® and Oracle® Software' e-CRFs and in a Clinical Trial Management System (CTMS) named IMPACT MySites, that supports online and offline monitoring activities and the collection of associated data during site visits[16] by CRAs.

5.2.3. Characterization of the Clinical Trials

Until the 31 of May of 2011, the CRA trainee performed activities within18 different clinical trials as per Tables 3 and 4 bellow.
Information regarding projects in which the training was focused is described in Appendix B.

Table 3 –Characterization of the Clinical Trials where CRA trainee was involved.

CT Ref. No.	Therapeutic Area	Phase	Randomized?	Blind	Comparator?
1	Dermatology	IIIb/IV	Yes	Open Label	Yes
2	Pneumology	III	Yes	Double Blind	Yes
3	Ophthalmology	IIIb	Yes	Single Blind	Yes
4	Cardiology	IV	Yes	Double Blind	No
5	Proctology	II	Yes	Single Blind	No
6	Cardiology	II	Yes	Double Blind	No
7	Infectious Diseases	III	Yes	Double Blind	Yes
8	Nephrology	III	Yes	Open Label	Yes
9	Ophthalmology	IV	Yes	Double Blind	Yes
10	Oncology	II	Yes	Open Label	Yes
11	Oncology	III	Yes	Double Blind	No
12	Oncology	II	Yes	Open Label	Yes
13	Ophthalmology	IV	No	Open Label	No
14	Cardiology	III	Yes	Double Blind	Yes
15	Allergology	II	Yes	Double Blind	No
16	Neurology	III	Yes	Double Blind	No
17	Rheumatology	III	Yes	Double Blind	No
18	Neurology	III	Yes	Double Blind	Yes

Table 4 – Details of Global Distribution of Clinical Trials where CRA trainee was involved.

CT Ref. No.	Type of Client	International Study?	Multicentre?
1	Multinational CRO	Yes	Yes
2	Multinational CRO	Yes	Yes
3	Multinational CRO	Yes	Yes
4	Multinational CRO	Yes	Yes
5	Local Sponsor	No	Yes
6	Local Sponsor	No	Yes
7	Multinational CRO	Yes	Yes
8	International Sponsor	Yes	Yes
9	International Sponsor	No	Yes

10	Multinational CRO	Yes	Yes
11	Multinational CRO	Yes	Yes
12	Multinational CRO	Yes	Yes
13	International Sponsor	Yes	Yes
14	Multinational CRO	Yes	Yes
15	Multinational CRO	Yes	Yes
16	Multinational CRO	Yes	Yes
17	Multinational CRO	Yes	Yes
18	Multinational CRO	Yes	Yes

Of these 18 trials, the majority are international, multicentre, randomized, double blind trials, as observed in Tables 3 and 4. It is also possible to verify that the CRA trainee worked with several types of sponsors/clients, which enriched her experience and capacity of adaptation to the different SOPs, communication and working methodologies. Of the 18 CTs, only 3 were conducted locally and of these, only one belongs to an International Sponsor.

In what concerns to clinical trials phases, of the 18 studies that were characterized per phase, 5 were phase II, 9 were phase III, 1 was phase III/IV and 3 were phase IV. In comparison to data from Eurotrials, it is possible to observe that in both cases, phase III clinical trials represent the largest percentage. Nevertheless, according to Figure 11, no studies were performed in phase I, and phase IV studies were less common than phase II.

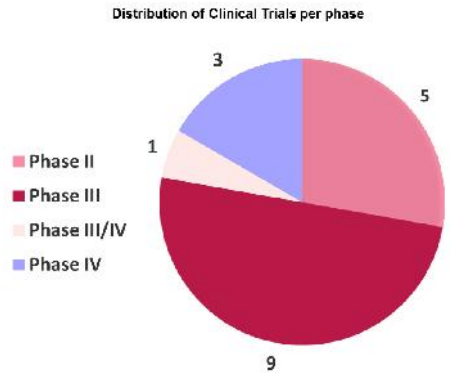


Figure 11 - Distribution of Clinical Trials where CRA trainee was involved according to study phase.

The activities developed within each study were different according to the clinical trial stage (feasibility, qualification, initiation, monitoring and end of study), study protocol, sponsor and study sites.
Figure 12 outlines an overview of the stages of the Clinical trial life cycle, from Project Initiation approval (Sponsor) until the development of the Clinical Study Report (CSR) and CSR submission to Competent Authorities (Project Conclusion).

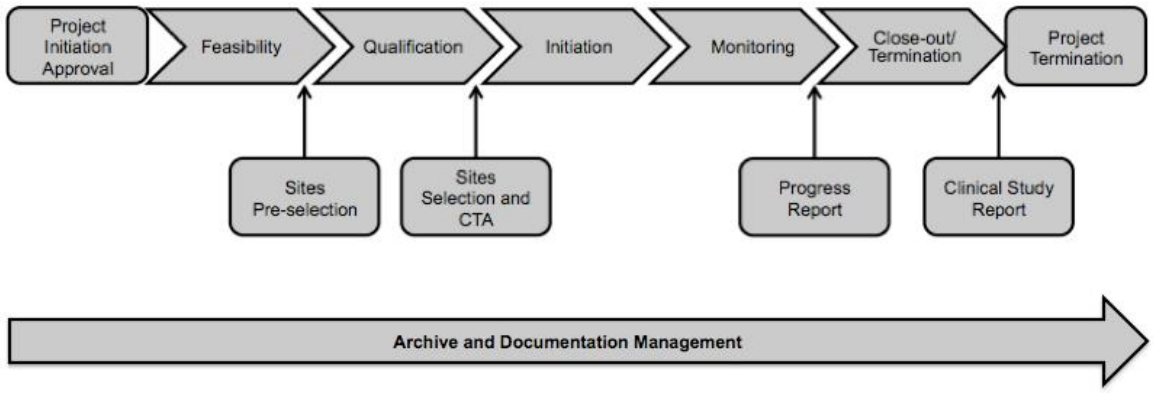


Figure 12 - Clinical Trials Life Cycle.

During the 9-month period, many different activities from the overview mentioned in Fig.12 were performed as CRA Trainee. In Figure 13, it is possible to observe that Qualification was the only stage not covered during the training since the projects where the CRA was involved were not in this specific phase of the process.

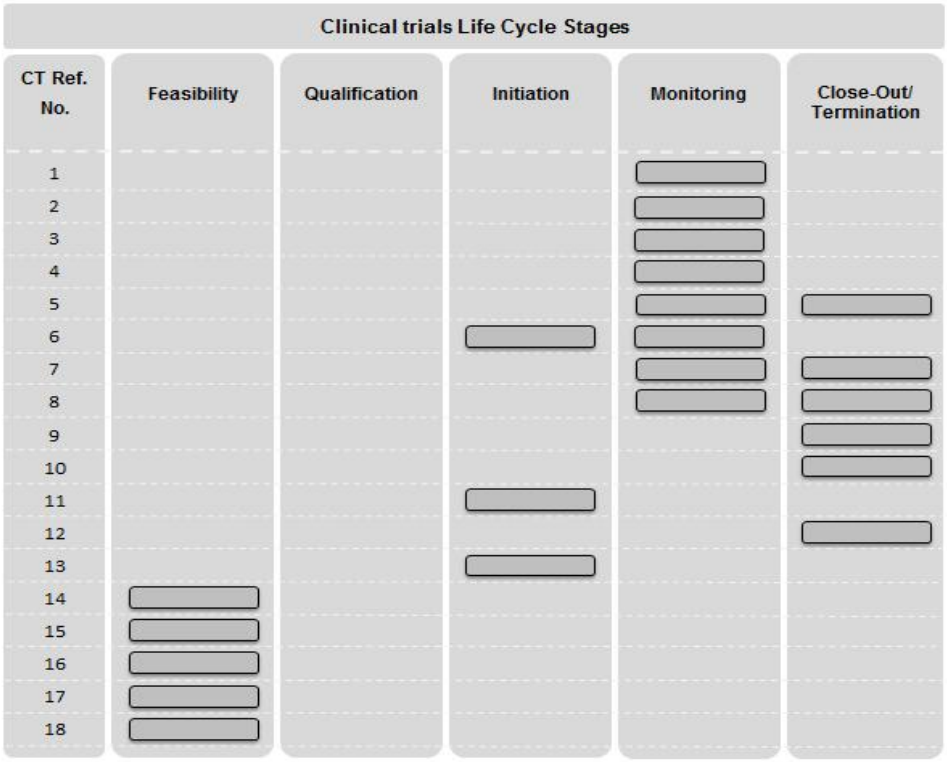


Figure 13 - Overview of developed activities within Clinical Trials Life Cycle.

In Appendix C it is also possible to have an overview of the training activities developed per month within the several Clinical Trials.

The following sections describe the important steps in clinical trials monitoring along with the CRA trainee experienced activities by the.

5.2.4. Archive and Documentation Management

"Documentation of research activities must be securely retained to provide evidence of activities"[17], for example, in case of a regulatory inspection or a sponsor representative audit.

In a clinical trial, there are three major documentation archives: Investigator File (IF), Pharmacy File (PhF) and Trial Master File (TMF). The IF and PhF are kept in the investigational where study is performed and in the related pharmacy, respectively. Such Files include study and site specific documents. PhF is part of IF and must include mainly, information on investigational product and related

records. The TMF contain all study essential documentation as well as specific documents from all investigational sites and other relevant documents, when applicable.

Every clinical trial should have a TMF Maintenance Plan or similar document where all procedures to be performed regarding study file management must be described. It must include information about who is responsible for keeping the files, where TMF physical archive is located, if there is local and/or central files, the frequency of documents shipment to the central file and which procedures should be followed, if applicable, among others.
In some of the 18 clinical trials, original documents were sent frequently to a central TMF while, for others, TMFs were kept locally until the study termination. Independently of the TMFs locations (central or local) it was essential to continually update the TMF and keep a checklist with all documents archived. The CRA trainee was able to verify that such checklist tool was essential for ensuring that all documentation was traceable and also for supporting in the identification of documents to be obtained from the investigational sites.

Based on the different clinical trials “age”, different approaches on filing were able to be followed. In some cases TMF was strictly paper, located in Eurotrials under effective CRA control, while for the most recent ones, all documents are archived electronically. This later cases were more challenging since the effective TMF was located in a different region of the world only accessible through portals or other internet tools, less controllable by the CRA and more dependent on other project teams work.

5.2.5. Feasibility

This process relates the stage where the sponsor or designee launches a Feasibility Study Assessment (FSA) in order to select the best sites/countries to participate in a clinical trial.
Considering that Eurotrials is a CRO, in general the first contact regarding this FSA comes from CRO or Sponsor directly. This request may include minimum

information on the study protocol, indication, IP and main inclusion/ exclusion criteria and the feasibility questionnaire (FQ). Although sometimes the sponsor gives names and contacts of potential investigators, it can also be requested to the CRO to refer some names.

The next step is to contact potential investigators, via e-mail or telephone, in order to introduce the study and ask for their interest in receiving more information and answering the feasibility questionnaire. In cases where the potential investigators are interested, a Confidentiality Disclosure Agreement is signed between both parts (if required by Sponsor). Feasibility questionnaire and protocol or protocol summary, as applicable, is then sent to sites. CRA must be able to support investigators with any question about the questionnaire and must follow-up with sites so that they answer the FQ within predefined timelines.

After FQs are completed and returned, Sponsor evaluates them and on the basis of the answers given pre-selects the most suitable sites for that specific clinical trial. It may be necessary to request for additional sites answers if sponsor cannot decide only based on the information collected in the first FQ and some additional questions are performed.

The CRA trainee participated in 5 clinical trials that were infeasibility stage. It was a very interesting and challenging step of the training due to several reasons:

- The difficulty to contact the potential investigators
- Make them answer the questionnaires that can sometimes be very exhaustive, in very tight timelines
- Make them deliver the necessary documents (CDAs and FQs)

The CRA Trainee verified that although the timeline is usually reasonable, in practice, it becomes really stressful to get all needed FQs answered on time. Investigators are very busy and the support provided by the CRA can only be over the phone since at this stage the CRA usually does not have sponsor approval to go to the sites. Nevertheless it is important to highlight that the

scientific interest of the information that is provided during this stage is directly linked with the initial Investigator interest and the FQ response rate from sites. It was also realised that this Feasibility stage may represent the chance of additional studies coming to Portugal and consequently have further projects services contracted to Eurotrials.

Once sponsor selects the sites/countries according to FQs results, the project usually moves to the next stage, the Qualification of the sites.

5.2.6. Qualification

Qualification is one more step in the process of selecting investigators and clinical sites to conduct the trial. This step is not always performed due to previous experience with a site/investigator or due to allocation of this responsibility to other company (or even the sponsor). The objective of this process is to select investigators who have the experience, interest in participating in the study, and are able to execute the trial as planned. The potential investigator should be able to recruit patients within the projected time period for subject enrolment, and should have a qualified research team and adequate clinical research facilities to carry out the research"[(18)].

The qualification phase usually requires a visit to the investigational site to verify the information transmitted by investigator on the feasibility questionnaire. This is a very important visit for ensuring appropriate site selection and for the future study conduction.

Unfortunately, it was not possible for the CRA trainee to prepare or participate in a qualification visit. Nevertheless, it is expected to perform this type of visits during next months, as there are some trials in which feasibility phase is ending.

5.2.7. Clinical Trials Application to National Authorities

In Eurotrials, there is a specific group, the CT Start-up Team that is responsible for the process of application of documents to INFARMED - the Competent

Authority (CA), CEIC - Central Ethics Committee (Central EC) and CNPD - the National Data Protection Authority.

In Portugal, the initial application of a CT must be submitted to INFARMED, CEIC and CNPD. The CT application to these authorities should be performed in parallel and their approval timelines are summarized in Figure 14.

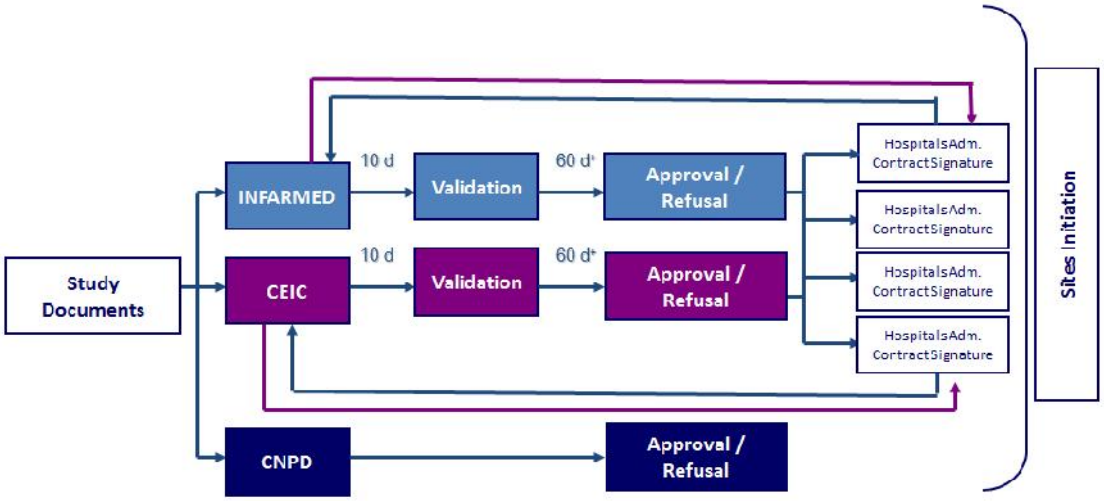


Figure 14 – Approval timelines of a Clinical Trial Application.

CEIC and INFARMED Application

There are no deadlines defined for the initial CT application to the Central EC. The EC meeting dates are always on the first Friday of each month. Considering the 60 days for review of a new Clinical Trial Application and the validation period (10 days maximum) – it is possible to estimate when the CT Approval will be expected. The CRA trainee realised that this information is crucial for the remaining planning of the clinical trials activities. In many cases this forecasted date is requested by Sponsor or CRO project team prior to the effective CT application is performed.

Following the Submission to Central EC, the internal EC process is:

1. Validation by the Central EC (clock starts counting 60 days)
2. Possible Questions by the Reviewer (clock stops until questions are answered, and after this, it starts again)

3. Reviewers send the Clinical Trial Submission to the next Plenary Session (EC meeting dates provided above)
4. Conditional Approval is granted (This is a general study Approval and being Conditional means that it will remain as so, until central EC receives the signed Contracts with each site, after which they will send the final Approval)
5. Notification of signed Contracts (can be for one site or several sites)
6. Final Approval is granted (per site or several sites, but will always be site-specific Approval, which enables SIVs to be performed)

Portuguese central EC only issues the favorable opinions for initial submissions and substantial amendments on their plenary meetings. This means that in case of questions raised it is very important that the answers to those questions are provided to Central EC until one week prior to their plenary meeting. Despite the clock stops during that period, from CRO and Sponsor side the time never stops and the CRA Trainee was able to verify that the Start-up Team must be able to provide adequate clarifications (through amended ICFs, Declarations or other remarks, as applicable) within the previewed deadlines, otherwise an additional month may be needed for Central EC to assess the responses provided to their clarifications and the correspondent approval in the next plenary session may be obtained. Consequently that somehow simple step may have a significant impact on the delay of the study initiation.

As ICF must be submitted to EC in the local language, the customization (including translation process) of the Model ICF should start as early as possible.

Contract negotiations with study sites are generally performed in parallel with the application process although some institutions require EC approval before signing and even negotiating the contract. Nevertheless, at least a draft version of contracts and a draft budget of study costs must be available for EC submission.

Regarding the CA, the approval process is similar to the described for Central EC however the approval can be quickest due to their more frequent meetings.
EC questions usually focus on Informed Consent Form (ICF) wording, study rationale and design while CA questions focus on the IMP.

The CRA trainee was involved in the application of a new clinical trial to CEIC and INFARMED. From the several activities involved in this process, the CRA trainee may refer specifically the support to the National Coordinator in the elaboration of an Ethical Assessment Statement draft.
Overall, this CT application gave the CRA trainee the possibility of following and becoming more familiar with study contracts and all other essential documents needed for the CT application to Portuguese authorities.

CNPD Application

The National Data Protection Authority, do not have, by law, any established timelines for the approval of a clinical Trial application. Yet, in general usually this authority takes 3 months to approve the data collection within a specific clinical trial.

In addition to initial and substantial amendments application to Central EC, CA and CNPD, other notifications need to be performed to the several authorities during the implementation and conduction of a clinical trial.
The CRA Trainee was able to be involved in some of those notifications, that based on the flow of occurrence within a CT are mentioned in sections 5.2.11, 5.2.13 and 5.2.15 bellow.

5.2.8. Investigator Meetings

Investigator meetings (IMs) are an important opportunity for investigators involved in a clinical trial to be trained in study protocol, meet other investigators, share opinions and experiences, learning about potential problems before they occur, ensure harmonisation of study procedures and clarify potential questions.

Usually, investigators, other sites staff and project team members from sponsor and/or CRO attend this kind of meetings.

Investigator meetings may include all global study sites or be organised on a local basis. IMs can occur before clinical trial initiation and/or during the trial and must address training in protocol, investigational product handling, safety aspects, Laboratory and Interactive Voice Response System (IVRS), GCP guidelines, and data recording. Pre-initiation IMs aim to prepare team sites in trial-specific procedures, including data introduction in the CRF. IMs organized during the clinical trial aim to give updated information regarding the study to investigators and train new investigators in the trial[(3)].

During CRA training, the trainee was involved in the organization of 2 investigator meetings and will have the opportunity to participate in one of them, a pre-initiation IM of one of studies that is still in application. This IM, only for Portuguese sites, will be presented by Sponsor and by the CRA trainee and will be a challenging activity as it will be the first time the CRA trainee attends this kind of meetings and as the responsible CRA for the trial.

5.2.9. CRA Training Meetings

CRA training meetings are events similar to Investigator Meetings but only CRAs are present.
The CRA trainee will attend a CRA meeting in June 2011, in which she will be trained in study protocol and procedures. This training will be crucial for the CRA trainee as she will have to speak about some procedures in the previously mentioned IM that will be occurring soon after that. This training will also be essential for ensuring that appropriate training was made for the site initiation visits (SIVs) that are expected to occur in September of this year.
Such meetings are considered as project specific trainings and need to be also documented in the individual training records.

5.2.10. Initiation

Study initiation is a critical step in a clinical trial and can only be performed after all INFARMED, CEIC and CNPD requirements have been fulfilled as well as site Administrative Board approval of the Clinical Study Agreement is obtained. The following essential documentation must be obtained before the clinical trial initiation visit may be performed:

- Authorizations from INFARMED, CEIC and CNPD
- Ethics Committee members list
- Curriculum vitae of all site members involved in the trial
- Local laboratory certification and its normal ranges (when applicable)
- Last approved versions of protocol and its amendments
- Confidentiality Agreement and signature page of protocol and amendments signed by Principal Investigator
- Site/Investigator contract with Sponsor executed by all parties
- Site declaration regarding adequacy of facilities and human resources
- Any other additional required document according to the study, site and sponsor.

On the Site Initiation Visit, the CRA must train the several site team members on the protocol and study procedures, safety, IP handling and appropriate records to be used, specific laboratory, nurse and imaging procedures and all additional documents and forms related with the trial. This is a very demanding visit for the CRA and is essential that the CRA is well prepared and has a deep knowledge of the study, to be able to provide the right information during the training of the different site team members. The training provided to the site staff during this visit is very important for ensuring compliance with the protocol, GCP guidelines and patients safety.

The CRA trainee had the opportunity to prepare and be present in an initiation visit in one of the clinical trials – cardiology trial. It was possible to understand how important is to prepare and to be capable to adapt the presentation of the

initiation visit according to the site staff present in each moment of the SIV – investigators, nurses, laboratory technicians and pharmacists.

5.2.11. Notification of inclusion of the first patient to Competent Authorities

During the training experience, CRA trainee was asked to notify INFARMED and CEIC about the inclusion of the first patient in a clinical trial for a site.

After study initiation, the first patient included in the study in Portugal must be notified to CEIC and INFARMED. Moreover the first patient included in each Portuguese site should also be notified. The first patient included in a site is defined according to the date in which the first ICF in that site is signed by a patient, regardless patient randomization or not.

5.2.12. Monitoring

Monitoring visits are an important step to evaluate site performance and the focus of the CRA in patients' safety and quality of data. CRA needs to:

- Evaluate the compliance to the protocol and the implementation of protocol amendments
- Verify that patients Informed Consent was correctly obtained
- Evaluate medication compliance through drug accountability
- Verify the occurrence of adverse events and serious adverse events and their notification according to local legislation timelines
- Perform source data verification (SDV), namely compare the information recorded in CRF with the source documents like patient chart notes, patients exam reports, nurse notes, etc.
- Evaluate temperature and humidity logs
- Update the Investigator File and Pharmacy File
- Collect essential documents from sites (example: Curriculum Vitae from the study team)
- Train new study team members or re-train study members, if necessary

- Evaluate patient recruitment, including revision of exclusion and inclusion criteria
- Verify if confidentiality of patients personal data is respected
- Confirm that only qualified/trained people work in the study and that they were authorized by principal investigator (according to the authorization log)
- Confirm that resources and equipment are still adequate and obtain appropriate documentation, as applicable.
- Evaluate if pending issues from previous visits were solved and follow them until resolution is available
- Discuss study status with Principal Investigator and applicable site team members

Sometimes it is not possible to perform all the above activities in the same monitoring visit due to the number of pending issues from previous monitoring visits, number of subjects, SDV backlog and availability of study team.

If appropriate the CRA must re-schedule another monitoring visit with the site in order to be able to review all the pending items and verify the overall site performance.

All these activities performed by the CRA must be in accordance with the Study Monitoring Plan. This plan defines all monitoring requirements, frequency and standards applicable to the specific clinical trial.

During the training period the CRA trainee had the opportunity to be present in some monitoring visits that were performed with the CRA supervisors that were also the responsible CRAs for the different studies. Within the several sites visited the CRA Trainee was able to verify that some sites were more organized and had more availability and human resources than others. In these monitoring visits the CRA trainee performed the following activities:

- Investigator File and Pharmacy File review and update

- Queries and pending issues resolution
- Verification of the occurrence of any protocol deviation
- Drug accountability
- Preparation of medication shipment to return to Sponsor for destruction
- Verification of new AEs existence
- Verification of data loggers (temperature and humidity logs)
- Source Data Verification
- Collection of some documents from sites
- Confirmation if the new ICF version was signed by patients
- Status with site teams in order to get feedback about possible difficulties, forms unavailable at sites and any other issues

In addition to the site monitoring visits, a great variety of other in-house monitoring activities were also performed:

- Contact with sites and Sponsor (including status updates)
- Quality Control checks, archiving documents and sending them to central file
- Prepare monitoring visits
- Prepare monitoring visit reports
- Write and send confirmation and follow-up letters
- Prepare and participate in a Sponsor audit
- Develop a clinical trial file checklist
- Prepare Investigator and Pharmacy Files
- Remote Monitoring of e-CRF and follow-up queries
- Supporting in investigator meetings preparation
- Collection of essential documents from sites
- Evaluate site recruitment and propose recruitment enhancement actions
- Prepare payments to sites
- Support the activities for the development of a Clinical Study Report

In future, it is expected to perform further monitoring visits more autonomously and considering also the recent involvement in some projects that are in the monitoring phase.

5.2.13. Elaboration of a Progress Report

Progress Reports should be submitted annually, or more frequently, to Central EC. This document is normally written by investigators and is a summary of the clinical trial status[19]. The CRA trainee supported the responsible CRA in the development of such document for one clinical trial - in cardiology. This Progress report will be reviewed and signed by study National Coordinator before notification to Sponsor and Authorities.
This report included topics like, present study status, CT application and approval timelines, number of patients included, completed and discontinued, SAEs as well as any protocol deviations and actions implemented by the sites.

This document is very important to provide more frequent overview of the study conduct and compliance of the several sites to the authorities, especially in longer trials, like the oncology ones.

5.2.14. Close-out/Termination

The close-out visit to a site usually takes place after Database lock, although it can be performed before its definitive closure upon Sponsor and Principal Investigator agreement. It is the last CRA visit regarding the study to the sites and should be performed only when all data queries related to site are resolved. It is important to notify local authorities about study termination and archive the respective documentation and correspondence.

The ideal situation would be to schedule the visit with all team members of the site to finalize pending issues and to inquire them about their opinion on site performance and overall satisfaction with the study[20].

In a clinical trial, the close-out visits' objective is to ensure that:

- All queries are resolved
- All adverse events are documented and reported appropriately
- All randomization codes have been returned from blinded sites without being opened (excepted in reported emergency situations), if applicable
- Drug accountability is complete and accurate or any deviations documented
- All study medication was reconciled and returned
- Shipment receipts are completed and accurate
- The regulatory binder is updated
- Specific documentation from site is up-to-date (e.g.. CVs, Laboratory normal ranges, Authorized Log and Monitoring Visit Log)
- The correct archive and maintenance of study files (a form must be signed by Principal Investigator to document his responsibility in the long term retention of files and the IF availability in case of Inspection)

"The correct archive and maintenance of study files" is an important issue in this stage. In some cases, an external company may be contracted to archive study files if the site is unavailable to keep them. According to ICH guideline E6, "essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product"[19]. Although, according to the Portuguese Decree-law no. 102/2007 of April 2 (20th Article), clinical trial essential documents must be retained for at least 5 years, typically, wherever files location, all study documents are usually kept archived for at least 15 years[3, 21].

One of the clinical trials in which activities were developed, was in termination phase and it was necessary to schedule, prepare and conduct the study close-out visits.

The major lesson learned was the importance of constantly updating site files, keeping a written registration on which documents were left at the site and which were collected and to have an updated list of all pending issues.

The CRA Trainee was able to verify that a complete and effective close-out visit of a clinical trial site is a good indicator of the quality of the monitoring activities throughout the study and of the site team commitment during the clinical trial.

5.2.15. Development of a Clinical Study Report

One of the most important documents in a clinical trial is the Clinical Study Report (CSR). The CSR is the document, after global completion or termination of a trial, where results and its interpretation are registered and conclusions, regarding the study design, statistical analyses performed, objectives accomplished, among other issues, are discussed.

The Clinical Study Report of a clinical trial (or summary of the CSR) must be notified within 1 year after the trial global conclusion to the authorities, INFARMED and CEIC.

The trainee developed a first draft of an abbreviated CSR, under supervision and guidance of the Eurotrials Medical Writer (MW) according to Sponsor requests, guideline ICH E3[19] (Structure and Content of Clinical Study Reports) and FDA Guidance for Industry[20] (Submission of Abbreviated Reports and Synopses in Support of Marketing Applications). Since the CRA trainee was not involved in the project from start, the major difficulties found were to understand the project and to identify which information should be included in the report. On the other hand, it was excellent to understand how data collected from patients in CRFs is transformed in “clean data” and finally in conclusions that have impact in data submitted to authorities for new Investigational products or new indications approvals.

5.2.16. Project Hand-over

Despite the training period did not contemplate this specific topic, the CRA trainee considered this to be also a relevant item within the CRA activities.
The Project hand-over is the transition of a project and all its relevant issues, like: essential documentation, status of sites and available reports, pending issues, contacts of team members, patient status, location of documents, applicable SOPs, Forms and regulations, communication plan among others, in any time of its lifecycle, from current person/team to a new CRA/team. The main objective of this process is to ensure that a new resource approved by Sponsor or designee and adequately trained in the project will ensure the project continuation, so no gaps in information or procedures may occur during the handover. The CRA trainee experienced a project hand-over. The previous CRA stopped her participation in the study due to personal reasons and it was given the opportunity to the CRA trainee to become the responsible CRA for that study. The CRA Trainee was able to understand that the transition of the study is a sensitive issue that demand a significant amount of time to be dedicated to this activity. Per personal experience it was understood that as much as possible both the current and the new CRA should perform a monitoring visit to each of the sites together so that applicable study site issues may be discussed and transitioned on site and appropriate site team introduced to the new CRA.

5.2.17. Audits

An audit is a “systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)”[(19)].
There are two types of audits: internal and external. Internal audits are performed within the company quality management system implementation and are important to assure the quality of the studies activities and of the overall processes performed by the company staff.

External audits are audits performed by the Sponsor or delegated auditors to the clinical trials or other activities implemented by Eurotrials or to Eurotrials Quality Management System, typically designated as system audits.
During the training period a Sponsor audit was performed to the study file of one of the studies in which the CRA Trainee was working on. This audit was a great opportunity to understand how important is to have a good file tracking and to learn how to prepare an audit. It also demonstrated how to improve job performance in future cases and it was an excellent chance to have a better idea of Sponsor way of working, values, culture and objectives.

Since Eurotrials is an ISO 9001:2008 certified company, during the training period the CRA Trainee was also able to participate in the preparation and follow-up of an ISO surveillance audit. The focus of this type of audits is different from a Sponsor audit since the ISO auditor wishes to ensure that the ISO Standards are followed overall and that globally the Company continues to develop its activities towards quality improvement.

6. DISCUSSION AND CONCLUSION

The 9-month experience as a Clinical Research Associate in Eurotrials was fantastic. For this opinion contributed not only the understanding of the CRA job itself but also a good work environment that is due to an excellent interaction between all collaborators at Eurotrials.

Clinical Trials department of Eurotrials is a great place to learn. All opportunities are given to all collaborators, including the trainees. Everyone is available to support and explain, and the interaction between all departments allows understanding the real flow of information that would not be possible if, for example, Regulatory Affairs Department, Data Management and Biostatistics did not exist.

The transdisciplinar experience within Data Management and Biostatistics Departments were important to realise, what are their responsibilities, how important their activities are and their influence in the job of the CRA. However, the trainee would like to have this kind of opportunity in other Eurotrials departments, for e.g., Pharmacovigilance and Quality, and it would be excellent if the duration of these interactions could be extended. It would be a good way to know Eurotrials collaborators' work and identify new interests and other professional development areas.

In what concerns the monodisciplinar experience, it was really positive and confirmed how interesting and challenging this job is. All knowledge acquired during the Degree in Biomedical Sciences and during the Master in Pharmaceutical Biomedicine were reviewed and many topics became clearer. It is recognised that the structure and curricular units of this master were essential to have a better understand of real-life activities developed within a Research Project. There is still knowledge to be acquired and updated, as this is an area in constant changing.

However, the trainee had the opportunity to be involved in 18 studies, in different therapeutical areas, stages, procedures and client culture. This experience, although intense, increased the range of skills acquired in a short notice period (9months).

The most important outcome of this training was the increased interest for this area and the improvement observed during this period. During the training period the CRA trainee was invited by Eurotrials to assume the role of CRA and was assigned with on-going clinical trials with specific responsibility and accountability for the trials activities.

In the near future, this will allow to gain experience in many other activities that are usually under CRA responsibility and that were not possible to develop during the training. Mainly to perform additional sites visits as well as to become more autonomous. The clinical trials presently assigned and the perspective of assignment/involvement in future trials are very promising and challenging, aspects that are essential for personal motivation and career progression. This way, there will be the opportunity to acquire more knowledge and experience as a CRA and also to grow as a person.

Even considering that this was the first internship experience between Eurotrials and University of Aveiro, it may be important to consider, for future trainings, to have an initial well-structured plan with training objectives in order to keep a better track of the activities experienced. For example, the plan should be discussed between Eurotrials and University of Aveiro in order to have a better understanding of what activities would be important to develop and assure that initial training objectives are accomplished.

Despite being included within the company daily work and being considered a regular collaborator, the CRA trainee also considered that the Project Manager delegated for the supervision and coaching of the trainee could have a better performance in this activity if the above-mentioned plan was available.

Still, the greatest difficulty observed during the training was the capacity to reconcile the training with Master units study and evaluations and also the report development. It was also very challenging the need to improve communication skills and learn how to work in a team, in a daily-basis.

In a lifelong learning basis, the CRA trainee will continuously try to improve her personal and professional skills taking into account the already acquired background impossible to achieve without the support of University of Aveiro and Eurotrials.

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8. APPENDICES

8.1. APPENDIX A

Glossary[19, 24, 25]

Adverse Event (AE) - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Audit - A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Case Report Form (CRF) - A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study - Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report - A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in

which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Clinical Research Organization (CRO) - A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Electronic Case Report Form (e-CRF) - an electronic form that does the same thing a paper CRF does. The clinical site types the data into an electronic form that gets electronically submitted to the sponsor. Essentially, the sponsor is removing a (paper-based) step and pushing the data entry from their internal (Data Management) group to the clinical site.

National Coordinator - An investigator assigned the responsibility for the coordination of investigators at different centres, in a country, participating in a multicentre trial.

Good Clinical Practices (GCP) - A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Informed Consent - A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

International Conference on Harmonization (ICH) - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Investigational Product - A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Inspection - The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the Sponsor's and/or Clinical Research Organizations (CROs) facilities or at other establishments deemed appropriate by the regulatory authority(ies).

Investigator - A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Monitoring - The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Protocol - A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Protocol Amendment - A written description of a change(s) to or formal clarification of a protocol.

Sponsor - An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Standard Operating Procedures (SOPs) - Detailed, written instructions to achieve uniformity of the performance of a specific function.

Statistical Analysis Plan (SAP) - A document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Trial Site - The location(s) where trial-related activities are actually conducted.

8.2. APPENDIX B

Clinical Trials Experience

Clinical Trials Monitoring activities:

1. **May 2011/ongoing – Dermatology –** CRA trainee in a multicentre, open label, randomized, Phase IIIb/IV exploratory clinical trial in patients with moderate to severe plaque psoriasis.

2. **April 2011/ongoing – Pneumo-Oncology –** Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of therapy in patients with stage IIIB/IV or recurrent non-small cell lung cancer after failure of first line chemotherapy – Development of activities as CMA trainee (Clinical Monitoring Associate) of the study.

3. **April 2011/ongoing – Ophthalmology –** In-house CRA Support activities in a 2 year randomized, single-masked, multicentre, controlled phase IIIb trial in patients with macular edema and visual impairment secondary to Diabetes Mellitus.

4. **February 2011/ongoing – Cardiology –** Multicentre, double-blind, randomized, placebo-controlled, parallel group, prospective, event driven phase IV study on Pulmonary Arterial Hypertension. Co-monitoring activities related with study documentation, namely preparation of Central File documentation and correspondent Quality Checks.

5. **September 2010/ongoing – Proctology –** In-house CRA co-monitoring activities on a phase II, multicentre, randomized, single-blind, placebo-controlled study in patients with chronic anal fissure, namely audit preparation, Trial Master File revision, support in close-out visits preparation and sponsor communications.

6. **September 2010/ongoing – Cardiology –** co-monitoring activities in a exploratory, phase II, randomized, double-blind, parallel group, placebo-controlled study in patients with Diabetes Mellitus type 2 and Dyslipidaemia, treated with statins, namely in Investigator Site Files preparation, support to Site Initiation Visit.

7. **February 2011/April 2011 – HIV –** Co-monitoring activities in a phase III, multicentre, randomized, double-blind, double-dummy study in patients infected with HIV-1.

8. **February 2011/March 2011 – Nephrology –** In-house CRA Support activities in a Prospective, randomized, multicentre, open label phase III study to evaluate the efficacy and safety of Immunosuppression following a heart-beating cadaveric renal transplantation.

9. **February 2011 – Ophthalmology –** Design of a Clinical study report of a phase IV, multicentre, randomized, double-blind, active-controlled study in patients with open-angle glaucoma or ocular hypertension.

10. **November 2010/March 2011 – Oncology –** In-house CRA Support activities in a phase II, open-label, multicentre, randomized, positive-controlled study in patients with Metastatic Colorectal Cancer, namely on Essential Documentation revision and final Country File documents reconciliation.

11. **October 2010/January 2011 – Oncology –** Support to CRA in a phase III, multicentre, randomized, double-blind, placebo-controlled study in patients with Metastatic Gastric Adenocarcinoma, namely sites' start-up activities, related sites communication and Sponsor regular status updates.

12. **October 2010/December 2010 – Oncology –** Support to CRA in a phase II, open-label, multicentre, parallel group, randomized study in patients with Breast Cancer, namely in Trial Master File reconciliation for close-out activities.

13. **September 2010 – Ophthalmology –** CRA support activities on a prospective pilot study in patients with cataracts, namely in site Initiation Visit documentation preparation.

Feasibility Studies Activities:

14. **May 2011/ongoing – Cardiology –** feasibility activities on a phase III, multicentre, randomized, double-blind, parallel-group study in Patients with Type 2 Diabetes Mellitus with Inadequate Glycaemic Control.

15. **April 2011/ongoing – Allergology –** feasibility activities on a phase II, multicentre, randomized, double-blind study, with subcutaneous immunotherapy at different doses in parallel-groups and placebo-controlled, in patients with Rhinoconjuntivitis ± Asthma sensitized to *Phleum Pratense*.

16. **April 2011/ongoing** – **Neurology** – feasibility activities on a multicentre, phase III randomized, double-blind, 3-Arm, placebo-controlled, 78-week parallel group study to assess the efficacy and safety of the therapy in subjects with Mild to Moderate Alzheimer's Disease.

17. **January 2011/ongoing – Rheumatoid Arthritis –** feasibility activities on a phase III, multicentre, randomized, double-blind, placebo-controlled study in patients with active Rheumatoid Arthritis.

18. **October 2010/December 2010 – Neurology –** Co-monitoring activities on a phase III, multicentre, randomized, double-blind, double-dummy, positive-controlled study in patients with Epilepsy, namely sites contacts and follow-up until feasibility questionnaire was obtained.

8.3. APPENDIX C

Developed Activities during the Training

Training Plan - Eurotrials Clinical Trials Department									
Study Activities	2010				2011				
	Sep	Out	Nov	Dec	Jan	Feb	Mar	Apr	Mai
Study Specific Documents Familiarization									
Protocol	X	X	X		X	X		X	X
Informed Consent Form	X								
Case Report Form	X					X		X	X
ICH/Legislation/SOPs	X				X	X		X	X
Feasibility									
Feasibility Contacts	X	X	X	X	X	X	X	X	X
Feasibility Visits									
Feasibility Status to Sponsor		X	X	X	X	X	X	X	X
Study Implementation									
Pre-study Visits (Preparation, execution and report)									
Site Contracts preparation								X	X
Submission to CNPD									
Submission to CEIC								X	X
Submission to INFARMED								X	X
Study Monitoring									
Investigator and Pharmacy Files	X		X						
Trial Master File	X		X		X				
Initiation Visit (Preparation, execution and report)			X						
Monitoring Visit (Preparation, execution and report)			X			X			
Safety Information Notification (AEs/ ASR)									
Newsletters							X		
Progress Reports (INFARMED)									X
In-house Monitoring (communication with Sponsor and sites, status reports, CRF revision and, management of queries, drug, supplies and documents)		X	X	X	X	X	X	X	X
Study documents translation			X						
Investigator Meeting Preparation		X							X
In-house Monitoring (Laboratory)		X	X	X	X	X	X	X	X
Drug accountability		X				X			
Study Payments to sites			X						X
Audit (Preparation, execution and follow-up)					X	X	X	X	
Study Close-out/Termination									
Investigator and Pharmacy File			X	X					
Trial Master File			X	X					
Close-out Visit (Preparation, execution and report)			X	X					
Data Management and Database Close-out									
Statistical Analysis									
CSR (Clinical Study Report)						X			